DETAILED ACTION

Status of the Application

1. Applicant's response filed on April 7, 2011 is acknowledged. Claims 251-287 and 625 are currently pending. In the response, claims 261, 271-274, 284, 286, and 287 were amended.

The following include new grounds of rejection necessitated by Applicant's amendments to the claims. Any previously made objections or rejections not reiterated below have been withdrawn. Applicant's arguments filed on April 7, 2011 have been fully considered and are discussed in the "Response to Arguments" section. Since the new grounds of rejection were necessitated by Applicant's amendments, this office action is made **FINAL**.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/896,897, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112

for one or more claims of this application. The earlier-filed '897 application does not provide adequate support for claims 251-287 and 625 of the instant application, because it does not teach primer extension using primers containing 3' terminal nucleotides that comprise nucleotide analogues with substitutions on the 2' position of the ribose ring. Accordingly, claims 251-287 and 625 have not been accorded benefit of the earlier-filed '897 application, and the instant application filing date (**October 24, 2003**) has been used for prior art purposes.

Information Disclosure Statement

3. Applicant's submission of an Information Disclosure Statement on April 7, 2011 is acknowledged. A signed copy is enclosed.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 284-287, and 625 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Nam et al. (Proceedings of the National Academy of Sciences, USA (2002) 99(9): 6152-6156; cited previously) and further in view of Laird et al. (EP 1 201 768 A2; cited previously).

These claims are drawn to method for copying a library of target nucleic acids using primers that are complementary to a homopolymeric sequence in the library of target nucleic acids and contain at least one nucleotide analogue at the 3'-terminus having a modification at the 2' position of the ribose ring.

Lin teaches methods for generating cDNA libraries from cells (see Figure 1 and column 2, line 42 – column 3, line 16).

Regarding claims 251, 264, and 281, Lin teaches a method for synthesizing one or more copies of a library of target nucleic acids comprising:

(a) providing:

(i) a library of target RNA molecules (see column 6, lines 10-17 and column 2, lines 45-51; see also Figure 1, step a),

(ii) primers comprising sequences complementary to homopolymeric sequences in the library of nucleic acid targets (see Figure 1, column 2, lines 52-56, column 6, lines 17-21 and lines 60-65),

(iii) synthesizing reagents for the synthesis of a nucleic acid copy (see column 2, lines 52-55 and column 6, lines 15-24), and

(iv) addition reagents for addition of a non-inherent universal detection target (UDT) comprising terminal deoxynuclsotidyl transferase (TdT) (column 2, lines 58-65 and column 6, lines 25-32),

(b) annealing the primers to the homopolymeric sequences in the library of target nucleic acids (see Figure 1, column 2, lines 52-56, and column 6, lines 17-21),

(c) extending the annealed primers using the synthesizing reagents to generate at least one copy of the target nucleic acids (Figure 1, column 2, lines 52-56, and column 6, lines 17-21), and

(d) adding a non-inherent UDT to the extended primers (see Figure 1, column 2, lines 58-65, and column 6, lines 25-32, where the polyG tail is added to the extended primers).

Regarding claim 252, Lin teaches that the library of targets is isolated from a biological source (column 6, lines 15-17).

Regarding claims 254 and 256, Lin teaches that the homopolymeric sequences, which are poly A sequences, are present prior to the isolation of the library of targets from the biological source (see Figure 1, step a and column 6, lines 15-25).

Regarding claim 261, Lin teaches that the synthesizing reagents comprise Taq DNA polymerase (see column 7, line 5, for example).

Regarding claims 262 and 263, Lin teaches that the method of claim 251 further comprises:

(a) providing additional synthesizing reagents for synthesizing a complementary copy of the copy obtained in step (c) (see Figure 1, step c and column 6, lines 43-49)

(b) separating the nucleic acid target from the first nucleic acid copy (see Figure 1, step c and column 6, lines 43-49, where synthesis of the complementary copy by Pwo polymerase inherently results in separation of the target from the first copy)

(c) synthesizing the complementary copy using reverse primers complementary to sequences in the UDT (Figure 1, step c and column 6, lines 43-49, where the poly(dC) primer is taught).

Regarding claims 269-272, the forward and reverse primers taught by Lin comprise a production center, since they contain T7, T3, or SP6 promoter sequences which function to produce multiple copies of the target nucleic acid sequence (see Figure 1 and column 6, lines 15-65; see also column 3, lines 28-31).

Regarding claim 273, Lin teaches that the method of claim 271 further comprises:

(a) providing reagents for RNA transcription comprising RNA polymerase (see Figure 1, step d, column 2, line 66 – column 3, line 4, and column 6, lines 35-55),

(b) providing dNTPs and NTPs (column 6, lines 35-55), and

(c) creating a transcript (column 6, lines 35-55 and Figure 1, step d).

Regarding claim 275, Lin teaches condcucting the transcription reaction in the presence of labeled nucleotides to generate labeled transcription products (column 5, lines 19-23).

Regarding claim 284, Lin teaches that the sequences complementary to the homopolymeric sequences in the library of nucleic acid targets are comprised of T (see Figure 1, for example).

Regarding claim 285, Lin teaches that the homopolymeric segment is comprised of poly A (see Figure 1, column 3, lines 32-39, and column 6, lines 15-65).

Regarding claim 625, Lin teaches a method for synthesizing a copy of at least one nucleic acid target comprising:

(a) providing:

(i) at least one nucleic acid target (see column 6, lines 10-17 and column 2, lines 45-51; see also Figure 1, step a),

(ii) at least one primer or nucleic acid construct complementary to a poly A sequence in the nucleic acid target, wherein the primer or nucleic acid construct comprises one or more terminal nucleotides at the 3' end (see Figure 1, column 2, lines 52-56, and column 6, lines 17-21), and

(iii) template-dependent synthesis reagents for the synthesis of a nucleic acid copy (column 2, lines 52-55 and column 6, lines 15-24),

(b) annealing the primer or nucleic acid construct to the target nucleic acid (see Figure 1, step b, column 2, lines 52-56, and column 6, lines 17-21), and

(c) synthesizing a copy of the target nucleic acid using the target nucleic acid as a template and extending the primer or nucleic acid construct using the synthesizing reagents (Figure 1, step b, column 2, lines 52-56, and column 6, lines 17-21).

Lin does not teach that the primers contain 3' terminal nucleotides that are substituted with nucleotide analogues having a modification at the 2' position of the ribose ring as required by claims 251, 259, 286, and 287. Lin also does not teach the use of chimeric primers as required by claim 260.

Nam teaches that oligo(dT) primers can produce spurious truncated amplification products during reverse transcription reactions due to their ability to hybridize to internal polyA sequences contained in the mRNA template in addition to the polyA tail of the mRNA template (pages 6153-6155 and Figure 1). Nam teaches that this problem may be reduced by including one or two "anchor" nucleotides at the 3' end of the oligo(dT) primers, which promote binding of the primers to the 3' polyA tail of the mRNA template rather than an internal polyA sequence (pages 6153-6154). Nam does not teach the use of primers having 3'-terminal nucleotides containing modifications at the 2' position of the sugar, however.

Laird teaches methods for conducting PCR amplification using modified primers (see abstract and paragraphs 12-18). Laird teaches that the disclosed modified primers increase the time required for initial primer extension, and thereby, reduce nonspecific amplification of the target nucleic acid (paragraph 37).

Regarding claims 251, 259, and 625, Laird teaches conducting PCR using primers in which 1-3 of the 3' terminal nucleotides are modified nucleotides selected from 2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides (paragraphs 12-18).

Regarding claim 260, Laird teaches that the primers may contain additional nucleotide analogues (paragraph 20).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Laird and Nam to the method of Lin. Since Nam taught that oligo(dT) primers, which were used in the method of Lin, could produce spurious truncated amplification products during reverse transcription reactions due to their ability to hybridize to internal polyA sequences contained in the mRNA template in addition to the polyA tail of the

mRNA template (pages 6153-6155 and Figure 1), the ordinary artisan would have been motivated to modify the primers of Lin to include the additional 1-2 terminal nucleotides taught by Nam, and, thereby, reduce the likelihood of non-specific extension occurring during the reverse transcription step in the method of Lin. An ordinary artisan also would have been motivated to further modify the primers used in the method of Lin such that 1-3 of the 3'-terminal nucleotides were 2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, or 2'-amino-nucleotides. An ordinary artisan would have been motivated to do so, since Laird taught that the presence of these modified nucleotides at the 3' terminus of an amplification primer reduced nonspecific amplification stemming from primer-dimer formation or non-specific hybridization of the primer (paragraphs 12-13, 28, 36-37, and 47, for example). The ordinary artisan would have had a reasonable expectation of success in applying the teachings of Laird and Nam to the method taught by Lin, since Laird and Nam taught that the synthesis of the disclosed primers was conducted using commercially available reagents and standard chemical synthesis methods known in the art (paragraphs 41-45 of Larid and 6152 of Nam). Regarding claim 286, when 1-3 of the nucleotide analogues taught by Laird are included in the primers suggested by Lin and Nam, nucleotide analogues are present in the homopolymeric portion of the primer. Also, regarding claim 287, when the additional one or two 3'-terminal nucleotide analogues suggested by Nam and Laird are incorporated into the oligo(dT) primers of Lin, the resulting primers possess at least one nucleotide that is different from those of the homopolymeric sequence.

Finally, attention is directed to MPEP 2142, which states that it is *prima facie* obvious to apply known methods to a similar method to improve the method in the same way. In this case, Lin teaches a "base method" that is very similar to the claimed invention. The primers used in

the method of Lin do not include the required nucleotide analogues. However, as evidenced by Laird, the claimed nucleotide analogues were known in the art to be useful for reducing non-specific amplification. Since, as evidenced by Nam, non-specific amplification was known to occur when primers having the same general features as those of Lin were used in reverse transcription reactions, the ordinary artisan would have been motivated to modify the primers of Lin to include the features identified by Nam and Laird as being capable of reducing non-specific amplification (*i.e.*, additional 3'-terminal nucleotides and nucleotides containing modifications at the 2' position of the ribose), and, based on the teachings of Laird and Nam, would have expected predictable results from the resulting primers. Thus, the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 284-287, and 625 are *prima facie* obvious over Lin in view of Laird.

6. Claims 253, 255, 257, and 258 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Nam et al. (Proceedings of the National Academy of Sciences, USA (2002) 99(9): 6152-6156; cited previously) and further in view of Laird et al. (EP 1201788; cited previously) and further in view of Kustu et al. (US 6,242,189 B1; cited previously).

These claims are drawn to the method of claim 252, wherein the library comprises copies of nucleic acids isolated from a biological source and comprising a homopolymeric sequence enzymatically added after isolation of the library from the biological source.

The combined teachings of Lin, Nam, and Laird render obvious the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 284-287, and 625, as discussed above.

These combined teachings of Lin, Nam, and Laird do not suggest that the library of nucleic acid targets is comprised of copies of nucleic acids isolated from a biological sample as required by claim 252. The combined teachings of Lin, Nam, and Laird also do not suggest adding a homopolymeric sequence to the library of nucleic acid targets using an enzyme, such as TdT, after isolation of the nucleic acids from the biological sample as required by claims 254, 255, 257, and 258.

Kustu teaches methods for selectively isolating bacterial mRNA from biological samples (see abstract and column 1, lines 45-59). Kustu teaches that bacterial mRNAs do not usually contain a 3' polyA tail, and therefore, these mRNAs cannot be distinguished from rRNA or tRNA by a common structural feature (column 1, lines 9-27). The method of Kustu comprises isolating bacterial mRNA from a biological sample and adding a homopolymeric polyA tail to the 3'-terminus of the isolated mRNA using TdT, a ligase, or polyA polymerase (column 1, lines 45-59 and column 2, line 10 – column 3, line 19). Kustu further teaches that the isolated mRNA can be amplified to permit for further analysis (columns 6-7).

It would have been *prima facie* obvious to apply the teachings of Kustu to the methods resulting from the combined teachings of Lin, Nam, and Laird. Since Lin taught that the disclosed methods were suitable for use with any type of cell sample, an ordinary artisan would have been motivated to utilize any desired cell type when practicing the methods of Lin, such as the bacterial cells described in Kustu, with a reasonable expectation of success. When using mRNAs isolated from bacterial cells as the library of nucleic acid targets in the method of Lin, as suggested by the teachings of Kustu, an ordinary artisan would have been further motivated to conduct the polyA tailing reaction described by Kustu in order to prepare the bacterial mRNAs

for the initial reverse transcription step in the methods of Lin. Thus, the methods of claims 253, 255, 257, and 258 are *prima facie* obvious in view of the combined teachings of the cited references.

7. Claims 265-268 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Nam et al. (Proceedings of the National Academy of Sciences, USA (2002) 99(9): 6152-6156; cited previously) and further in view of Laird et al. (EP 1201788; cited previously) and further in view of Willis et al. (US 6,858,412; cited previously) and further in view of Moran et al. (Nucleic Acids Research (1996) 24(11): 2044-2052; cited previously).

These claims are drawn to the method of claim 264, further wherein a terminator nucleotide is provided in a mixture comprising terminator and non-terminator nucleotides during the UDT addition step and the method further comprises synthesizing a copy of the nucleic acids obtained in the method of claim 251.

The combined teachings of Lin, Nam, and Laird render obvious the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 284-287, and 625, as discussed above.

The combined teachings of Lin, Nam, and Laird do not teach or suggest including a terminator nucleotide in the TdT tailing reaction as required by claims 265-268.

Regarding claim 266, Lin teaches that the non-inherent UDT is added to a nucleic acid copy by providing TdT and non-terminator nucleotides (Figure 1, step c and column 6, lines 35-55).

Regarding claim 267, Lin teaches that the method of claim 266 further comprises:

(a) providing additional synthesizing reagents for the synthesis of a complementary copy of the nucleic acid copy (column 6, lines 35-55, where Pwo polymerase synthesizes a complementary copy of the UDT-containing copy)

(b) separating the target nucleic acid from the first nucleic acid copy (see Figure 1, step c and column 6, lines 35-55, where upon synthesis of the complementary copy, the target is inherently separated from the first copy)

(c) synthesizing the complementary copy (Figure 1, step c and column 6, lines 35-55).

Willis teaches amplification-based methods of nucleic acid analysis (see abstract and column 4, line 50 – column 5, line 15). Regarding claims 265, 266, and 268, Willis teaches the use of terminal transferase to add chain-terminating nucleotides, such as ddNTPs or acyclic nucleotides, to prevent extension or amplification (see column 26, lines 40-45).

Moran teaches that polymerase-mediated DNA and RNA synthesis reactions often produce molecules with non-homogenous or ragged 3' termini due to spurious template-independent addition of nucleotides by the polymerase (page 2044). Moran teaches that this "complicates purification, may interfere with subsequent reactions, such as ligation, and wastes nucleotide substrates (page 2044, column 2)." Regarding claims 265-267, Moran teaches that, "addition of a single non-coding nucleotide analogue to the 5' terminus of the template DNA strand can result in much more efficient and specific termination at the desired site (3'-end of the product). The use of such 'terminator' nucleotides results in the production of cleaner RNA and DNA oligonucleotide products, often in greater yields, and with more efficient use of nucleotides (page 2044, column 2 – page 2045, column 1)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Willis and Moran to the method resulting from the combined teachings of Lin, Nam, and Laird. An ordinary artisan would have been motivated to include a terminator nucleotide, such as the dideoxy or acyclic nucleotides taught by Willis, in the terminal transferase tailing reaction taught by Lin, since Willis taught that these nucleotides prevented polymerase-mediated extension, and also since Moran taught that terminator nucleotides reduced template-independent addition of 3' terminal nucleotides by DNA and RNA polymerases (see column 46, lines 40-45 of Willis and pages 2044-2045 of Moran). An ordinary artisan would have been particularly motivated to minimize template-independent addition of nucleotides by the polymerase, since Moran taught that such addition "complicates purification, may interfere with subsequent reactions, such as ligation, and wastes nucleotide substrates (page 2044, column 2)." An ordinary artisan would have had a reasonable expectation of success in including dideoxy or acyclic nucleotides in the terminal transferase reaction taught by Lin, since Willis taught that terminal transferase could incorporate these nucleotides into nucleic acids (column 26, lines 40-45). Thus, the methods of claims 265-268 are *prima facie* obvious in view of the combined teachings of Lin, Nam, Laird, Moran, and Willis.

8. Claims 274 and 276 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Nam et al. (Proceedings of the National Academy of Sciences, USA (2002) 99(9): 6152-6156; cited previously) and further in view of Laird et al. (EP 1201788; cited previously) and further in view of Sousa et al. (US 5,849,546; cited previously).

These claims are drawn to the method of claim 271, wherein the RNA transcription step is conducted under conditions that result in a labeled DNA transcript or a labeled RNA/DNA chimeric transcript.

The combined teachings of Lin, Nam, and Laird render obvious the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 284-287, and 625, as discussed above.

Regarding claim 274, Lin teaches that the method of claim 271 further comprises:

(a) providing reagents for RNA transcription comprising RNA polymerase (see Figure 1, step d, column 2, line 66 – column 3, line 4, and column 6, lines 35-55)

(b) providing dNTPs and NTPs (column 6, lines 35-55)

(c) creating a transcript (column 6, lines 35-55 and Figure 1, step d).

Regarding claim 276, Lin teaches conducting the transcription reaction in the presence of labeled nucleotides to generate labeled transcription products (column 5, lines 19-23).

Lin does not teach the use of a mutated RNA polymerase for generation of a chimeric RNA/DNA transcript as required by claim 274.

Sousa teaches methods for synthesizing chimeric nucleic acid molecules using a mutant RNA polymerase (see abstract and column 4, line 53 – column 5, line 31).

Regarding claim 274, Sousa teaches providing reagents for RNA transcription comprising a mutated RNA polymerase, NTPs, & dNTPs and creating a chimeric DNA/RNA transcript (column 9, lines 41-46). Sousa further teaches that RNase A only cleaves RNA after a C or a U, and therefore, replacement of these rNMPs with dNMPs or other nucleotides resistant to nuclease cleavage would prevent this cleavage by RNase A (column 8, lines 55-67).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Sousa to the method resulting from the combined teachings of Lin, Nam, and Laird. An ordinary artisan would have been motivated to utilize the mutant RNA polymerase taught by Sousa to generate chimeric DNA/RNA transcripts, since Sousa taught that such transcripts displayed improved resistance to ribonucleases (column 8, lines 55-67). An ordinary artisan would have recognized that RNase degradation of the transcription product produced in step (d) of the method outlined in Figure 1 of Lin would be detrimental, since the method of Lin required a post-transcription PCR amplification step, and therefore, would have been motivated to minimize the possibility of such degradation by generating a chimeric DNA/RNA transcript as suggested by Sousa. Thus, the methods of claims 274 and 276 are *prima facie* obvious in view of the combined teachings of Lin, Nam, Laird, and Sousa.

9. Claims 277, 278, and 280 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Nam et al. (Proceedings of the National Academy of Sciences, USA (2002) 99(9): 6152-6156; cited previously) and further in view of Laird et al. (EP 1201788; cited previously) and further in view of Steffens et al. (Genome Research (1995) 5: 393-399; cited previously).

Claim 277 is drawn to the method of claim 273 and has been interpreted as requiring the synthesis of a copy of the RNA transcript generated by the method of claim 273. Claims 278 and 280 are drawn to the methods of claims 275 and 277, respectively, and require the use of a labeled nucleotide selected from a Markush group.

The combined teachings of Lin, Nam, and Laird render obvious the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 284-287, and 625, as discussed above.

Regarding claim 277, although Lin teaches labeling nucleic acid amplification products at multiple stages of the method (transcription and TdT tailing – see column 5, lines 19-23), Lin does not teach including labeled nucleotides in the final RT-PCR amplification step used to generate a copy of the RNA transcription product as required by claim 277.

Regarding claims 278 and 280, Lin teaches labeled nucleotides (column 5, lines 19-23), but does not teach specific examples of labels.

Steffens teaches the use of a nucleotide labeled with an infrared fluorophore for detection of nucleic acids (see abstract). Regarding claim 277, Steffens teaches including the labeled nucleotide in PCR reactions for incorporation into the resulting products (page 397, column 2). Regarding claims 278 and 280, Steffens teaches that labeling nucleic acids with this nucleotide permits highly sensitive detection with minimal background (page 394, column 1).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize the fluorescently labeled nucleotide taught by Steffens in the method resulting from the combined teachings of Lin, Nam, and Laird. An ordinary artisan would have been motivated to utilize the nucleotide taught by Steffens to label transcription products generated by the method resulting from the combined teachings of Lin, Nam, and Laird, since Steffens taught that labeling nucleic acids with this nucleotide permitted highly sensitive detection with minimal background (page 394, column 1). Also, as noted in MPEP 2144.07, the selection of a known material based on its suitability for the intended purpose is *prima facie* obvious in the absence of unexpected results. An ordinary artisan would also have been

motivated to label nucleic acid products generated at any point in the method resulting from the combined teachings of Lin, Nam, and Laird (*e.g.,* the final RT-PCR step) in order to monitor the yield at each step of the process. An ordinary artisan would have been motivated to do so, since Lin taught labeling nucleic acid products produced at multiple steps of the method (see column 5, lines 19-23). As noted above, an ordinary artisan would have been motivated to utilize the fluorescently labeled nucleotide taught by Steffens to conduct this labeling step, since Steffens taught that the nucleotide permitted sensitive detection of labeled nucleic acids with minimal background. An ordinary artisan would have had a reasonable expectation of success in using the fluorescently labeled nucleotide taught by Steffens, since Steffens expressly taught its use in PCR amplification (page 397, column 2). Thus, the methods of claims 277, 278, and 280 are *prima facie* obvious in view of the combined teachings of Lin, Nam, Laird, and Steffens.

10. Claim 279 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Nam et al. (Proceedings of the National Academy of Sciences, USA (2002) 99(9): 6152-6156; cited previously) and further in view of Laird et al. (EP 1201788; cited previously) and further in view of Sousa et al. (US 5,849,546; cited previously) and further in view of Steffens et al. (Genome Research (1995) 5: 393-399; cited previously).

Claim 279 is drawn to the method of claim 276, respectively, and requires that the labeled transcription products contain a particular type of label.

The combined teachings of Lin, Nam, and Laird render obvious the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 284-287, and 625, as discussed above. Also,

the combined teachings of Lin, Nam, Laird, and Sousa render obvious the methods of claims 274 and 276.

Regarding claim 279, Lin teaches labeling transcription products using labeled nucleotides (column 5, lines 19-23), but does not teach specific examples of labels.

Steffens teaches the use of a nucleotide labeled with an infrared fluorophore for detection of nucleic acids (see abstract). Steffens teaches including the labeled nucleotide in PCR and sequencing reactions for incorporation into the resulting products (pages 394-395). Steffens teaches that labeling nucleic acids with this nucleotide permits highly sensitive detection with minimal background (page 394, column 1).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize the fluorescently labeled nucleotide taught by Steffens in the method resulting from the combined teachings of Lin, Nam, Laird, and Sousa. An ordinary artisan would have been motivated to utilize the nucleotide taught by Steffens to label transcription products generated by the method resulting from the combined teachings of Lin, Nam, Laird, and Sousa, since Steffens taught that labeling nucleic acids with this nucleotide permitted highly sensitive detection with minimal background (page 394, column 1). Also, as noted in MPEP 2144.07, the selection of a known material based on its suitability for the intended purpose is *prima facie* obvious in the absence of unexpected results. In this case, an ordinary artisan would have had a reasonable expectation of success in using the fluorescently labeled nucleotide taught by Steffens in the labeling reaction of Lin, since Sousa taught that the disclosed mutant RNA polymerase was capable of incorporating several different types of modified nucleotides (see column 9, lines 21-40). It is also noted that no evidence of unexpected results has been

presented. Thus, the method of claim 279 is *prima facie* obvious in view of the combined teachings of Lin, Nam, Laird, Sousa and Steffens.

11. Claims 282 and 283 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Nam et al. (Proceedings of the National Academy of Sciences, USA (2002) 99(9): 6152-6156; cited previously) and further in view of Laird et al. (EP 1201788; cited previously) and further in view of Stinear et al. (Applied and Environmental Microbiology (1996) 62(9): 3385-3390; cited previously).

These claims are drawn to the method of claim 251, wherein the primers are immobilized on a solid matrix, such as a magnetic bead.

The combined teachings of Lin, Nam, and Laird render obvious the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 284-287, and 625, as discussed above.

The combined teachings of Lin, Nam, and Laird do not suggest the use of bead-immobilized primers as required by claims 282 and 283.

Stinear teaches a method for isolating and amplifying mRNA from a biological sample (see abstract). The method of Stinear comprises capture of mRNA present in the sample using a magnetic bead-immobilized oligo(dT) primer followed by RT-PCR (see abstract and pages 3385-3387). Stinear teaches that capture of a target nucleic acid present in a sample using magnetic bead-immobilized oligonucleotides results in a greater reduction of amplification inhibitors than conventional purification methods (page 3385). Stinear also teaches that "Magnetic beads are simple to use, do not require expensive equipment, and demonstrate a high level of recovery" (page 3388).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to practice the method resulting from the combined teachings of Lin, Nam, and Laird using magnetic-bead immobilized oligo(dT) primers. An ordinary artisan would have been motivated to do so, since Stinear taught that magnetic bead-based capture and amplification was associated with reduced co-purification of amplification inhibitors and was a rapid, inexpensive, and simple method for capturing and amplifying a target nucleic acid of interest (see above). Since Stinear taught that the disclosed magnetic beads were commercially available (page 3386), an ordinary artisan would have had a reasonable expectation of success in conducting the methods resulting from the combined teachings of Lin, Nam, and Laird using magnetic bead-immobilized primers as suggested by Stinear. Thus, the methods of claims 282 and 283 are *prima facie* obvious in view of the combined teachings of the cited references.

12. Claim 625 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nam et al. (Proceedings of the National Academy of Sciences, USA (2002) 99(9): 6152-6156; cited previously) in view of Laird et al. (EP 1201788; cited previously).

Claim 625 is drawn to a method for synthesizing a copy of a target nucleic acid using primers that are complementary to a homopolymeric sequence in the library of target nucleic acids and contain at least one nucleotide analogue at the 3'-terminus having a modification at the 2' position of the ribose ring.

Nam teaches a method for synthesizing a copy of at least one nucleic acid target comprising (see pages 6162-6153): (a) providing at least one nucleic acid targe5, (ii) at least one primer that is complementary to a poly A sequence in the nucleic acid target, wherein the primer

or nucleic acid construct comprises one or more terminal nucleotides at the 3' end, and (iii) template-dependent synthesis reagents for the synthesis of a nucleic acid copy, (b) annealing the primer to the target nucleic acid, (c) synthesizing a copy of the target nucleic acid using the target nucleic acid as a template and extending the primer using the synthesizing reagents.

Nam does not teach that the 3' terminal nucleotide(s) of the primer contain 2' substitutions to the ribose ring.

Laird teaches PCR amplification using modified primers (see abstract and paragraphs 12-18). Regarding claim 625, Laird teaches conducting PCR using primers wherein 1-3 of the 3' terminal nucleotides are modified nucleotides selected from 2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides (paragraphs 12-13). Laird teaches that the modified primers increase the time required for initial primer extension, and thereby, reduce nonspecific amplification of the target nucleic acid (see abstract and paragraph 37).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Laird to the method of Nam. Since Nam taught that the disclosed anchored oligo(dT) primers reduced, but did not eliminate, the production of undesirable truncated amplification products during reverse transcription reactions (pages 6153-6154), the ordinary artisan would have been motivated to modify the primers of Nam such that 1-3 of the 3'-terminal nucleotides were 2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, or 2'-amino-nucleotides in order to further improve the specificity of the amplification reaction. An ordinary artisan would have been motivated to do so, since Laird taught that the presence of these modified nucleotides at the 3' terminus of an amplification primer reduced nonspecific amplification stemming from primer-dimer formation or misextension of the primer (paragraphs

12-13, 28, 36-37, and 47, for example). The ordinary artisan would have had a reasonable expectation of success in applying the teachings of Laird to the method of Nam, since Laird taught that the synthesis of the disclosed primers was conducted using commercially available reagents and standard chemical synthesis methods known in the art (paragraphs 41-45). Attention is also directed to MPEP 2142, which states that it is *prima facie* obvious to apply a known method to a similar method to improve the method in the same way. In this case, Nam teaches a "base method" that is very similar to the claimed invention. The primers used in the method of Nam do not include the required nucleotide analogues at the 3' terminus. However, as evidenced by Laird, the claimed nucleotide analogues were known in the art to be useful for reducing non-specific amplification. Since Nam taught that the anchored oligo(dT) primers used in the disclosed method were still capable of generating non-specific amplification products, the ordinary artisan would have been motivated to modify the primers of Nam to include the features identified by Laird as being capable of reducing non-specific amplification (*i.e.*, nucleotides containing modifications at the 2' position of the ribose at the 3' terminus of the primer), and, based on the teachings of Laird, would have expected predictable results from the resulting primers. Thus, the method of claim 625 is *prima facie* obvious over Nam in view of Laird.

Response to Arguments

13. Applicant's arguments filed on April 7, 2011 have been fully considered.

Objection to claim 261

Applicant argues that the objection has been obviated by the claim amendments (page 10). This argument was persuasive, and, accordingly, the objection has been withdrawn.

Rejection of claims 284, 286, and 287 under 35 U.S.C. 112, second paragraph

Applicant argues that the rejections have been obviated by the claim amendments (pages 10-11). This argument was persuasive, and, accordingly, the rejections have been withdrawn.

Rejection of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 285-287, and 625 under 35 U.S.C. 103(a) as being unpatentable over Lin in view of Nam and further in view of Laird

In view of the amendments to claim 284, the rejection currently applies to claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 285-287, and 625.

Applicant first argues that the claimed invention is concerned with preventing unextended primers from undergoing addition of a non-inherent UDT by including one or more nucleotides at the 3' end of the primer other than deoxyribonucleotides, specifically ribonucleotides (pages 11-12). Applicant also argues that neither Laird nor Nam addresses the problem with which the invention is concerned (page 12).

In response to this argument, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In this case, as discussed in the rejection, the ordinary artisan would have been motivated to modify the oligo(dT) primers of Lin to include the additional one or two target-specific 3'-terminal nucleotides taught by Nam to be useful in reducing the production of truncated amplification products stemming from undesired priming from internal polyA sequences. Then, since Nam taught that the disclosed anchored oligo(dT) primers reduced, but did not eliminate, the production of undesirable truncated amplification

products during reverse transcription reactions (pages 6153-6154), the ordinary artisan would have been motivated to additionally modify the primers such that one to three of the 3'-terminal nucleotides were 2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, or 2'-amino-nucleotides in order to further improve the specificity of the amplification reaction as taught by Laird.

Applicant also argues that anchored primers as taught by Nam are not recited in the currently pending claims (page 12).

In response to this argument, it is first noted that oligo(dT) primers having one or two target-specific 3'-terminal nucleotides are not excluded from the claims. As written, the claims encompass primers having such nucleotides.

It is also noted that Nam is not non-analogous art as Applicant's arguments at page 12 suggest. It has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the prior art of Nam is in the field of Applicant's endeavor, specifically methods of creating nucleic acid libraries.

Finally, Applicant argues that there is no motivation to apply the teachings of Laird regarding nucleotide analogues to the method of Lin, because the method of Lin results in "essentially universal amplification of any and all sequences having a polyA tail" (page 13). Applicant also argues that, even if Nam is combined with the method of Lin, there is no reason to further apply the teachings of Laird regarding nucleotide analogues, because the problems

addressed by Laird (*i.e.*, reduction of primer dimers and spurious expression results derived from inappropriate priming) are not disclosed as problems by Lin (page 13).

In response to this argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007).

In this case, as discussed in the rejection, the teachings of the cited references provide the requisite motivation. It is noted that there is no requirement for Lin to explicitly describe problems associated with the disclosed method for motivation to exist. In this case, the ordinary artisan would have recognized from the teachings of Nam that the primers of Lin should be modified in the way taught by Nam to obtain the same benefit. Specifically, Nam provides evidence to suggest that the conventional oligo(dT) primers of Lin have the ability to produce undesirable truncated amplification products in addition to the desired full-length amplification products. Accordingly, the ordinary artisan would have been motivated to modify the conventional oligo(dT) primers of Lin to include one or two target-specific 3'-terminal nucleotides as taught by Nam to reduce the ability of the primers of Lin to hybridize to polyA sequences other than the desired 3'-terminal polyA sequence. The ordinary artisan would have been motivated to further include the specificity-enhancing modifications of Laird, since Nam

taught that the disclosed modification reduced, but did not eliminate, undesirable priming from internal polyA sequences.

Attention is also directed to MPEP 2142, which states that it is *prima facie* obvious to apply known methods to a similar method to improve the method in the same way. In this case, Lin teaches a "base method" that is very similar to the claimed invention. The primers used in the method of Lin do not include the required nucleotide analogues. However, as evidenced by Laird, the claimed nucleotide analogues were known in the art to be useful for reducing non-specific amplification. Since, as evidenced by Nam, non-specific amplification was known to occur when primers having the same general features as those of Lin were used in reverse transcription reactions, the ordinary artisan would have been motivated to modify the primers of Lin to include the features identified by Nam and Laird as being capable of reducing non-specific amplification (*i.e.*, additional 3'-terminal nucleotides and nucleotides containing modifications at the 2' position of the ribose), and, based on the teachings of Laird and Nam, would have expected predictable results from the resulting primers.

Since Applicant's arguments were not persuasive, the rejection has been maintained.

Rejections of claims 253, 255, 257, 258, 265-268, 274, 276-280, 282, and 283 under 35 U.S.C. 103(a) based on the primary combination of Lin, Nam and Laird

Regarding the rejections of claims 253, 255, 257, 258, 265-268, 274, 276-280, 282, and 283 under 35 U.S.C. 103(a) based on the primary combination of Lin, Laird, and Nam, Applicant argues that the additional secondary references cited in the rejections do not remedy the deficiencies in the primary combination of references with respect to independent claim 251 (pages 14-18). This argument was not persuasive, because, as discussed above, the combined

teachings of Lin, Nam, and Laird render obvious the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 284-287, and 625. Accordingly, the rejections have been maintained.

The rejection of claim 284 under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Lin, Nam, Laird, and Petrick has been withdrawn as being obviated by the amendment to claim 284. Accordingly, Applicant's arguments at page 18 regarding this rejection are moot.

Rejection of claim 625 under 35 U.S.C. 103(a) as being unpatentable over Nam in view of Laird

Applicant argues that the nucleotide analogues of Laird are only described in the context of PCR amplification, and, therefore, the ordinary artisan would not consider the disclosed specificity enhancements associated with the analogues to extend to the simpler primer extension reaction constituting the reverse transcription step of Nam (page 19). Accordingly, Applicant argues, there is no motivation to combine the references (page 19).

Applicant's argument was not persuasive, because the ordinary artisan would not have considered the specificity enhancement associated with the nucleotide analogues of Laird to be limited to PCR amplification reactions as Applicant argues. Laird hypothesizes that the disclosed nucleotide analogous increase priming specificity by increasing the time before the initial extension occurs (paragraphs 36-38). Laird also teaches that the disclosed nucleotide analogues are not only useful in PCR amplification and may be used in other amplification reactions (paragraph 46). Thus, the teachings of Laird do not suggest in any way that the observed improvements in specificity would only be observed in PCR amplification reactions and not in reverse transcription reactions, such as those of Nam. Based on the teachings of Laird, the

ordinary artisan would have considered the disclosed analogues to be generally useful for improving specificity in any reaction comprising a primer hybridization and extension step, *e.g.*, the reverse transcription reaction of Nam.

Since Applicant's arguments were not persuasive, the rejection has been maintained.

Conclusion

14. No claims are currently allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Angela M Bertagna/
Examiner, Art Unit 1637

/Young J Kim/
Primary Examiner, Art Unit 1637